UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,192	10/15/2003	Maurizio Pellecchia	BURNHAM.006A	3780

20995 7590 03/14/2006

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,192	PELLECCHIA, MAURIZIO	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 10-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 12/15/2005 is acknowledged. After entry of the amendment, claims 1-4 and 10-25 are pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 15, 17, and 22-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Pellecchia et al (Feb. 2002, J. Biomol. NMR) as evidenced by Minks et al (Biochem., 1999). This rejection is maintained for reasons of record and for reasons outlined below. The new claims have been added to this rejection due to applicants addition of new claims. Regarding new claims 15 and 24, Pellechia teach the labeled residues to be in the functional site of DHPR enzyme (page 167, second column, first full ¶).

Response to Arguments

Applicant's arguments filed 12/15/2005 have been fully considered but they are not persuasive. Applicants argue that: 1) Pellecchia et al does not specifically disclose the labeling of any tryptophan residues, but instead hypothesizes that such tryptophan residues might be selectively labeled; 2) that one of skill in the art would not know how to selectively label tryptophan residues, thus neither the Pellecchia et al nor the Goto et al article (referenced by Pellecchia et al) is enabling for selective labeling of tryptophan residues; 3) in a Rule 132

declaration, Dr. Pellechia states that the Pellecchia et al and Goto et al references do not enable one of skill in the art to selectively label tryptophan residues, and that the reference to Goto et al in his publication is a mistake.

Regarding 1) - 3) above, the arguments hinge upon whether one of skill in the art would know how to selectively label tryptophan residues in a polypeptide for NMR studies. Pellecchia references Goto et al as a general method for selectively labeling the amino acid of choice, which may be tryptophan. Goto et al disclose general methods for labeling the amino acid of choice, for example, the use of labeled precursors incorporated into certain residues, or auxotrophic host strains used in conjunction with labeled residues of choice to express a selectively labeled protein. Furthermore, Minks et al (published three years prior to Pellecchia et al) details a method to label human annexin V at the only tryptophan residue in the protein using any one of three ^{19}F tryptophan analogues. See page 10649, second column, first full ¶ to page 10650, second column, first ¶. Thus, one of skill in the art would know how to selectively label tryptophan residues and use them in the methods as disclosed by Pellechia et al. Also regarding 2), the declaration that the citation of Goto et al was a mistake is not relevant. One of skill in the art, reading the methods of Pellecchia et al, would take at face value that tryptophan could be labeled. Upon reading Goto et al, the skilled artisan would know that selectively labeling residues was well-established in the art, and therefore not a limiting step in practice of the Pellecchia et al methods.

Claims 1-4, 11, 13, 15-18, 20, and 22-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Fesik et al (U.S. patent 5,698,401, 1997, cited by applicants). This rejection is

maintained for reasons of record and for reasons outlined below. The new claims have been added to this rejection due to applicants addition of new claims. Fesik et al use $^{15}NH_4Cl$ to label proteins so "at least" the side chain(s) of tryptophan are labeled, see column 7, lines 11-17. The indole ring of tryptophan comprises an NH group which, absent evidence to the contrary, would incorporate the ^{15}N during the course of biosynthesis.

Applicant's arguments filed 12/15/2005 have been fully considered but they are not persuasive. Applicants argue that: 1) Fesik et al disclose "uniform" labeling of proteins versus "selective" labeling as found in the instant claims; 2) the term "selectively labeled" is known in the art to have a meaning distinct from uniformly labeled, and cite Pellechia et al and Goto et al as sources; 3) the term "selectively labeled" is distinguished from uniformly labeled in ¶'s [0011] and [0008] of the specification; 4) the definition of "selectively labeled" by the specification in ¶ [0021] does not cause selectively labeled to mean uniformly labeled, but rather is meant to address a situation wherein multiple occurrences of a particular residue are found in a protein and substantially all are labeled, rather than only one residue.

Regarding 1) - 4), the examination of applications is bound by what is disclosed in the specification, thus any specific definition of a term by the specification is controlling, regardless of other relatively obscure definitions in the art. Based on the definition of selective labeling given in the specification, Fesik et al is anticipatory for reasons of record. Regarding 3), neither ¶ provides a definition of selective labeling, but rather they describe uniform labeling applications (i.e. referencing Fesik et al, ¶ [0008]) and that there have been attempts to overcome difficulties in the art of uniform labeling with selective labeling of the methyl groups of specific amino acid residues (¶ [0011]). Neither [0008] nor [0011] define selective labeling as

found in ¶ [0021]. Regarding 4), the disputed passage reads (as quoted in the previous Office Action): "Selective labeling is defined as labeling substantially every occurrence of at least one particular amino acid throughout a polypeptide sequence." Thus, it is clear that the term "selective labeling" embraces labeling from one to every amino acid in the protein or polypeptide. Whatever applicants may have intended this definition to apply to, its literal meaning is quite clear and binding. There is no language to be found that the definition applies only to a situation where multiple occurrences of a particular labeled residue are found in a protein. Rather, in a confusing manner, the remainder of the paragraph lists a preferred embodiment wherein labeling "substantially every occurrence" is considered labeling "at least 50% of the particular amino acid or amino acids."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-14, 16, 18-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pellechia et al as applied to claims 1-4, 15, 17, and 22-24 above, and further in view of Minks et al (Biochem., 1999), Muchmore et al, Hibler et al, and Lemaster (all from Meth. in Enzymology, 1989). **This is a new rejection necessitated by amendment of the claims.**

The teachings of Pellechia et al are described above and applied as before. Pellechia et al do not specifically teach: labeling of the claimed target molecules wherein the peptide backbone is not labeled; the specific labeling of tryptophan with ^{1}H, ^{13}C, ^{15}N, or ^{19}F; and wherein the labeled moiety at the active site is tryptophan.

Minks et al teaches a method to label human annexin V at the only tryptophan residue in the protein using any one of three ^{19}F tryptophan analogues (see the above 102(a) rejection), in which the ^{19}F label is incorporated into the side chain of tryptophan (Scheme 1, page 10650). Minks teaches this single tryptophan residue to be at the active site of the protein (a calcium binding site), see page 10650, first column, first ¶. Minks also teaches tryptophan to be an attractive target for selective labeling because it is of low abundance in proteins and dominant chromophoric properties (page 10649, first column, first ¶).

Muchmore et al teaches a method to selectively label proteins at a defined residue(s) with ^{15}N, and that site may be tryptophan (see page 59, second full ¶ - page 61, second full ¶, and Table III). Absent evidence to the contrary, the ^{15}N labeled tryptophan is protonated (e.g. the hydrogen atoms are ^{1}H) and are considered labeled in a deuterated (^{2}H) background. This is important in determining the ^{1}H NMR spectra of proteins and side chains (page 44, second ¶), for example the ^{15}N-^{1}H peak of tryptophan indole in Fig. 1, page 45. Muchmore et al also teach the labeling can also be performed with ^{13}C labeled residues (page 46, first full ¶).

LeMaster teaches the deuteration of proteins in NMR for the purpose of improving ^{1}H spectra (page 23, first ¶) and that labeling is achieved using protonated amino acids in a deuterated background, i.e. selective protonation (page 23-24).

Hibler et al teach the isotopic labeling of proteins for NMR with ^{13}C, ^{1}H, or ^{2}H (see the entire document), and may be used to selectively label particular residues (¶ bridging pages 77-78), which may be tryptophan (¶ bridging pages 79-80).

The claimed method of detecting binding between a ligand and target molecule is essentially disclosed by Pellecchia et al with the exception of the specifics of isotopic residue labeling, and that the residue in the active site be tryptophan. The ordinary skilled artisan, seeking a method to analyze the binding of any given ligand to a given target protein, would have been motivated to use the ^{19}F, ^{13}C, ^{15}N, and ^{1}H residue labeling methods of Minks, Muchmore, LeMaster and Hibler et al with the binding methods of Pellecchia et al because Minks teaches tryptophan to be an attractive labeling target in general, while Minks, Muchmore, and Hibler teach tryptophan to be an important residue at active sites in specific proteins. Additionally, the different labeling methods utilizing different isotopes are taught to be well-known methods in the art with separate utility in determining either backbone, side chain, or position information. Thus, use of one labeling technique/isotope or another (or in conjugation) is a matter of design choice, influenced by the information desired and the protein/ligand in question. It would have been obvious for the skilled artisan to use the various methods because of the known benefit of deriving various points of structural information from the different techniques, and the choice would be determined by the amino acid residues present in the active site/binding site of the protein in question.

Furthermore, The ordinary skilled artisan, seeking a method to analyze the binding of any given ligand to a given target protein, would have been motivated to combine the deuteration methods of LeMaster with the ^{15}N-^{1}H labeling methods of Muchmore et al because Lemaster

teaches deuteration as a way of improving the ^{1}H spectra of such labeling. It would have been obvious for the skilled artisan to combine these methods for reasons cited above and because of the known benefit of improving experimental data.

Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 10, 12, 14, 19, 21 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fesik et al as applied to claims 1-4, 11, 13, 15-18, 20, and 22-25 above, and further in view of Minks et al (Biochem., 1999), Muchmore et al, Hibler et al, and Lemaster (all from Meth. in Enzymology, 1989). **This is a new rejection necessitated by amendment of the claims.**

The teachings of Fesik et al are described above and applied as before. Fesik et al do not specifically teach: labeling of the claimed target molecules wherein the peptide backbone is not labeled; the specific labeling of tryptophan with ^{13}C or ^{19}F.

The teachings of Minks, Muchmore, LeMaster, and Hibler et al are described above and applied as before.

The claimed method of detecting binding between a ligand and target molecule is essentially disclosed by Fesik et al with the exception of the specifics of isotopic residue labeling. The ordinary skilled artisan, seeking a method to analyze the binding of any given ligand to a given target protein, would have been motivated to use the ^{19}F and ^{13}C residue

labeling methods of Minks, Muchmore, LeMaster and Hibler et al with the binding methods of Fesik et al because Minks teaches tryptophan to be an attractive labeling target in general, while Minks, Muchmore, and Hibler teach tryptophan to be an important residue at active sites in specific proteins. In particular Minks teaches fluorinated tryptophans provide unique information regarding "hidden" chromophores such as tyrosines or phenylalanines, and thus are a sophisticated tool for studying protein-protein or DNA-protein interactions (Minks et al, page 10649, second column, first ¶). Additionally, the different labeling methods utilizing different isotopes are taught to be well-known methods in the art with separate utility in determining either backbone, side chain, or position information. Thus, use of one labeling technique/isotope or another (or in conjugation) is a matter of design choice, influenced by the information desired and the protein/ligand in question. It would have been obvious for the skilled artisan to use the various methods because of the known benefit of deriving various points of structural information from the different techniques, and the choice would be determined by the amino acid residues present in the active site/binding site of the protein in question.

Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

Any rejection not repeated in this Office Action is withdrawn.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER